

# The clinical efficacy and safety of vancomycin loading dose

## A systematic review and meta-analysis

Hekun Mei, MS, Jin Wang, MS, Haoyue Che, MS, Rui Wang, MS, Yun Cai, PhD\*

### Abstract

**Background:** The clinical significance of using vancomycin loading dose remains controversial. A systematic review and meta-analysis were performed to assess the clinical efficacy and safety of vancomycin loading dose in the treatment of infections.

**Methods:** The Pubmed, Embase, Web of Science, and Cochrane Library databases were searched from their inception up to 5 May 2019. Randomized controlled trials (RCTs) and other observational studies were included if they provided clinical outcomes or trough concentrations of vancomycin loading dose (20–30 mg/kg) and conventional-dose (10–20 mg/kg) in the treatment of infections. Achievement of therapeutic concentration (serum trough concentrations of vancomycin reached 15–20 mg/L before the second dose), clinical response (clinical improvement or culture-negative), nephrotoxicity (serum creatinine increase  $\geq 0.5$  mg/dL or  $\geq 50\%$  increasing from the baseline), other adverse events (including pruritus, flushing, rash, and/or red man syndrome), and mortality were analyzed. Heterogeneity was identified using the Cochrane  $I^2$  statistic, and  $P$ -value  $< .10$  or  $I^2$ -values  $> 50\%$  indicated significant heterogeneity. Pooled estimates of the intervention effects were determined by the odds ratios (ORs) and 95% confidence intervals (CIs) in Review Manager program, version 5.3.5.

**Results:** Two RCTs and 7 cohort studies including 2816 infected patients were selected for the analysis, in which serum trough concentrations of vancomycin following the use of vancomycin loading dose or other outcomes were available. Loading dose group had a significantly higher compliance rate of serum trough concentration of 15 to 20 mg/L (OR = 3.06; 95% CI = 1.15–8.15;  $P = .03$ ) and significantly lower incidence of nephrotoxicity (OR = 0.59, 95% CI = 0.40–0.87;  $P = .008$ ;  $I^2 = 29\%$ ) compared with control group. No significant difference was noted between loading dose group and control group in terms of other adverse events and clinical response (OR = 1.98, 95% CI = 0.80–4.93;  $P = .14$ ;  $I^2 = 0\%$ ). The use of vancomycin loading doses in patients can indeed increase the achievement of therapeutic concentration.

**Conclusion:** Vancomycin loading dose increases the achievement of therapeutic concentration without bringing extra risk of nephrotoxicity. However, well-designed large-scale RCTs remain needed to validate the clinical efficacy of vancomycin loading dose and to further evaluate other adverse reactions and mortality.

PROSPERO registration number CRD42018093927

**Abbreviations:** AUC<sub>0–24h</sub>/MIC = area-under-the-concentration-time curve over 24 hours/minimum inhibitory concentration, CIs = confidence intervals, CVI = continuous vancomycin infusion, ICU = intensive care unit, IVI = intermittent vancomycin infusion, MIC = minimal inhibitory concentration, MRSA = methicillin-resistant *Staphylococci*, NOS = Newcastle–Ottawa scale, ORs = odds ratios.

**Keywords:** clinical efficacy, loading dose, trough concentration, vancomycin

Editor: Lindsay Calderon.

HM and JW contributed equally to this work.

The authors alone are responsible for the content and writing of the paper.

This research was supported by the National Natural Science Foundation of China (No. 81573472 and No. 81770004), 13th Five-Year Plan of National Major Science and Technology Projects of China (No. 2018ZX09201-013), and Clinical Research Support Funding of PLA General Hospital (No. 2016FC-TSYS-2043).

The authors have no conflicts of interest to disclose.

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How to cite this article: Mei H, Wang J, Che H, Wang R, Cai Y. The clinical efficacy and safety of vancomycin loading dose. *Medicine* 2019;98:43(e17639).

Received: 28 May 2019 / Received in final form: 19 September 2019 /

Accepted: 25 September 2019

<http://dx.doi.org/10.1097/MD.0000000000017639>

## 1. Introduction

Vancomycin is a type of time-dependent antibiotic used to treat hospital-acquired infections or severe infections caused by susceptible strains of methicillin-resistant *Staphylococci* (MRSA).<sup>[1]</sup> Its antimicrobial efficacy depends on the time span during which the concentration of vancomycin in serum is higher than the minimal inhibitory concentration (MIC) between 2 administrations. When the concentration of vancomycin reaches 4 to 5 times of the MIC, the antibacterial efficacy is the highest.<sup>[2]</sup> Studies on animal infection models and clinical pharmacokinetics/pharmacodynamics (PK/PD) show that area-under-the-concentration-time curve over 24 hours/minimum inhibitory concentration (AUC<sub>0–24h</sub>/MIC) is the PK/PD parameter that predicts the clinical and bacteriological efficacy of vancomycin. When AUC<sub>0–24h</sub>/MIC  $\geq 400$ , bacteria can be cleared up and clinical symptoms can be relieved quickly.<sup>[3]</sup> However, in clinical practice, AUC<sub>0–24h</sub>/MIC is not routinely available to assess the clinical efficacy of vancomycin. Therefore, trough concentration is often used instead of AUC<sub>0–24h</sub>/MIC to predict the efficacy of vancomycin, because trough concentrations of vancomycin at

15 to 20 mg/L can effectively achieve  $AUC_{0-24h}/MIC \geq 400$ .<sup>[4,5]</sup> When vancomycin concentration is lower than 10 mg/L, bacteria cannot be effectively removed and vancomycin-resistant bacteria arise, leading to prolonged hospital stay and increased mortality rate.<sup>[6-9]</sup>

Recently, the use of vancomycin has increased due to increased MRSA infection rates. However, many patients were found having sub-therapeutic vancomycin concentrations in serum following initial dosing.<sup>[4]</sup> At the same time, vancomycin-resistant *Enterococci* and *Staphylococcus aureus* were found in patients. Thus, it is urgent to reconsider the dose of vancomycin in clinical application and use it more effectively. To rapidly reach an effective therapeutic concentration of vancomycin and optimize  $AUC_{0-24h}/MIC$ , a vancomycin loading dose of 25 to 30 mg/kg (based on actual body weight) in adults and 20 to 25 mg/kg in children is recommended for critically ill patients.<sup>[10]</sup> However, the safety and effectiveness of vancomycin loading doses in clinical applications remain to be fully evaluated. The purpose of this systematic review and meta-analysis was to systematically assess the currently available data in literatures regarding clinical applications of vancomycin loading dose to validate the clinical efficacy of vancomycin loading dose in the treatment of infections and to provide a reference for clinical medication.

## 2. Methods

### 2.1. Literature search

The Pubmed, Embase, Web of Science, and Cochrane Library databases were searched from their inception up to 5 May 2019. The terms used for the search were “vancomycin” and “loading dose.” In addition, the references of the initially identified articles, including relevant review papers, were also manually screened for related articles. No language restrictions were applied for literature search.

### 2.2. Study selection

The protocol of this study can be found at PROSPERO with the registration number of CRD42018093927.<sup>[11]</sup> The preferred reporting items for systematic reviews and meta-analysis statement were strictly followed. Randomized controlled trials (RCTs) and cohort studies that provided serum trough concentrations of vancomycin following the use of vancomycin loading dose or other outcomes in the treatment of infections were considered eligible. Studies that focused on pre-clinical research, laboratory research, and epidemiology were excluded. Studies in which the control group or loading dose group included 10 patients or fewer, studies on oral vancomycin use or nonhuman data, and studies that lacked the control group for standard use of vancomycin were also excluded. Two investigators (HKM and JW) independently carried out the literature search and study selection. The disagreements between the 2 investigators were resolved by consulting a third investigator (YC). Final consensus was obtained among all investigators.

### 2.3. Data extraction and evaluation

The 2 investigators (HKM and JW) independently extracted the relevant data and assessed the risk of bias. The following data were extracted from each study:

- (1) author(s) and year of publication;
- (2) country;

- (3) type of study;
- (4) baseline characteristics of the population;
- (5) type of infection;
- (6) number of patients enrolled;
- (7) dosing regimen (including loading dose and comparator);
- (8) efficacy;
- (9) reported adverse effects.

The modified Newcastle–Ottawa scale (NOS) was used to evaluate the quality of each included studies.<sup>[12]</sup> Studies with a NOS score  $< 3$  were classified as poor quality studies and excluded from this meta-analysis. Studies were ranked on the basis of their quality of evidence according to the US preventive Services Task 1996 rating system.<sup>[13]</sup> Level I studies were RCTs. Level II-1 studies were controlled studies, with patients acting as their own controls or with a parallel control group. Level II-2 studies were cohort or case-control designs. Level II-3 studies were multiple time series or exceptional descriptive articles. Level III studies were expert opinion, descriptive studies, and case reports.

### 2.4. Statistical analysis

Achievement of therapeutic concentration was the primary outcome we assessed. The secondary outcomes were: clinical response, nephrotoxicity, other adverse events, and mortality.

All statistical analyses were carried out using the Review Manager program, version 5.3.5 (Cochrane Collaboration, Oxford, United Kingdom). The heterogeneity of the results from included studies was assessed using Chi-square test of heterogeneity and the  $I^2$  measure of inconsistency. A Mantel–Haenszel random-effect model was used to assess the odds ratios (ORs) and 95% confidence intervals (CIs) for all primary and secondary outcomes throughout the meta-analysis. Heterogeneity was investigated through subgroup analysis, as defined above.  $P$ -values  $< .05$  were considered statically significant. Since the present study is based on the published data, ethical approval and informed consent are not applicable.

## 3. Results

### 3.1. Literature search

After literature search, we identified 1052 articles from 4 databases and another 4 articles from the references. In total, 73 relevant full-text articles were screened. In these articles, 19 reviews were excluded from the analysis because they were not original studies. In the remaining 54 articles, 45 articles were excluded, including 21 articles on pre-clinical studies and epidemiology, 18 studies lacking a control group, and 6 studies on irrelevant topics. Finally, 2 RCTs (158 patients) and 7 other studies (2658 patients) were included in the systematic review and meta-analysis.<sup>[14-22]</sup> The literature search and study selection process are shown in Figure 1.

### 3.2. Study characteristics

The main characteristics of the included studies are shown in Table 1. The quality of the 2 RCTs was evaluated by the Cochrane risk of bias tool, and the results showed that the quality of these 2 RCTs was pretty high (Fig. 2). One of the RCTs that was carried out in children aged 2 to 18 years was double-blind study, and the other RCT studied the application of loading dose in emergency department patients. Among the rest 7 studies, 2 of the observational studies were prospective cohort studies, 1 study

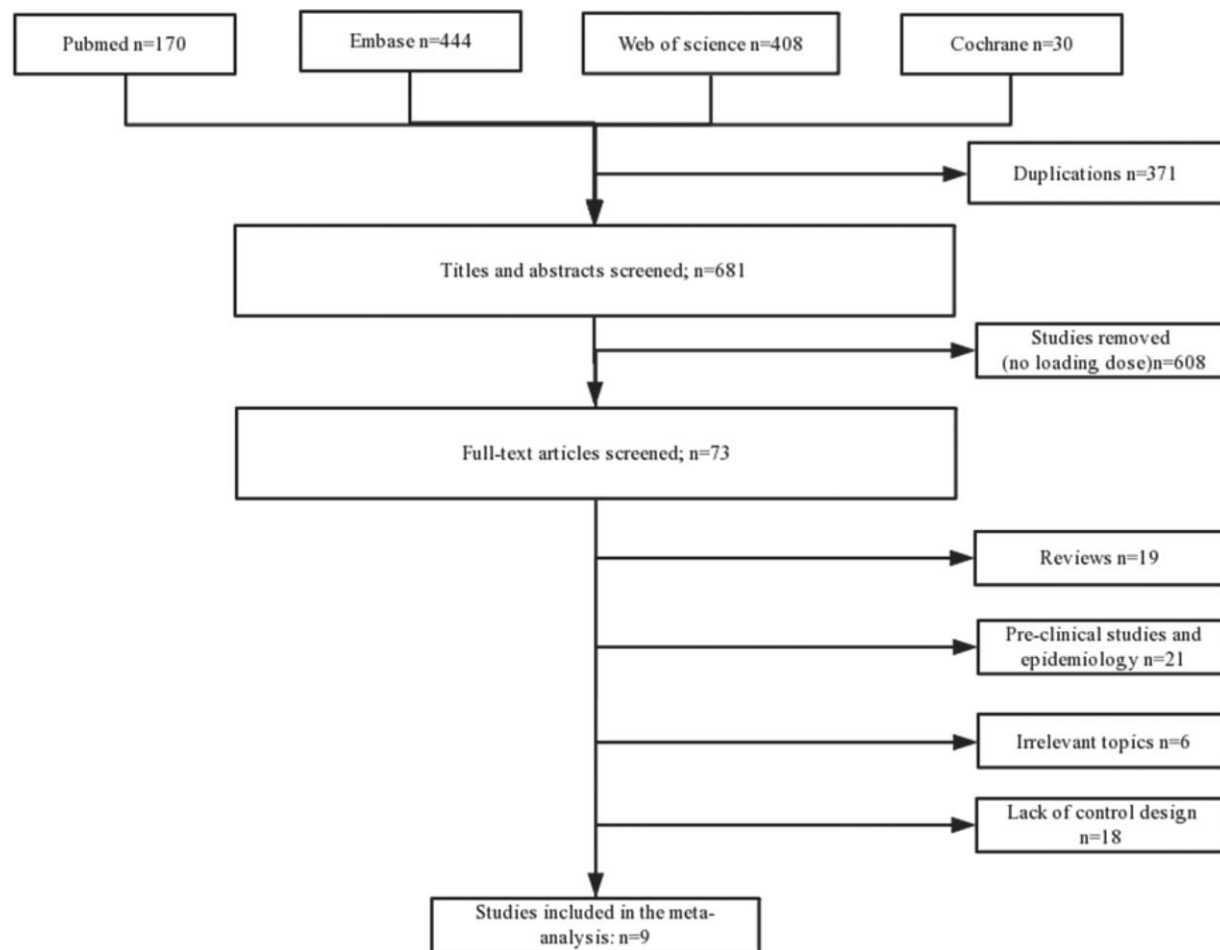


Figure 1. Flowchart of the article selection process.

conducted both retrospective and prospective evaluation and compared the results with each other. The subjects of 2 included studies were critically ill patients. Other studies included intensive care unit (ICU) patients, sepsis patients, patients with severe renal impairment, emergency department patients, hospitalized hemodialysis patients, and MRSA infected patients. The quality of the included studies was assessed by NOS, and the results showed that most studies had a score of 7 to 9 (Table 2).

### 3.3. Achievement of therapeutic concentration

As shown in Figure 3, the overall achievement of therapeutic concentration was significantly higher in loading dose group than in control group (6 studies; 1304 patients; OR=3.06 [95% CI=1.15–8.15];  $P=.03$ ;  $I^2=76\%$ ). In RCTs subgroup, the number of cases that achieved 15 to 20 mg/L vancomycin serum trough concentration was significantly higher in loading dose group than in the control (OR=15.22; 95% CI=[2.74–84.60];  $P=.002$ ;  $I^2=0\%$ ). In non-RCTs subgroup, the number of cases that achieved the target trough concentration of vancomycin was also higher in loading dose group than in control group, but the difference was not statistically significant (OR=1.96; 95% CI=[0.81–4.77];  $P=.14$ ;  $I^2=73\%$ ).

### 3.4. Nephrotoxicity

Two RCTs and 3 cohort studies (2532 patients) compared vancomycin exposure-associated nephrotoxicity between vancomycin loading dose group and the control group. The number of patients who suffered from nephrotoxicity was significantly lower in loading dose group than in control group (OR=0.59; 95% CI=[0.40–0.87];  $P=.008$ ;  $I^2=29\%$ ) and analysis of non-RCTs subgroups also showed significantly lower incidence in loading dose group (OR=0.53; 95% CI=[0.39–0.73];  $P<.0001$ ,  $I^2=13\%$ ). However, no significant differences were identified between vancomycin loading dose group and the control group in RCTs subgroups (OR=1.48; 95% CI=[0.23–9.53];  $P=.68$ ;  $I^2=40\%$ ) (Fig. 4).

### 3.5. Other adverse events

In addition to nephrotoxicity, the common adverse events of vancomycin exposure also included pruritus, flushing, and/or rash. In the included studies, only 2 RCTs (158 patients) compared other adverse events between vancomycin loading dose group and control group, and no significant differences were observed between the 2 groups (OR=1.98; 95% CI=[0.80–4.93];  $P=.14$ ;  $I^2=0\%$ ) (Fig. 5). In most cases, vancomycin was infused over 1 hour or at a rate less than 1000 mg/h to prevent red man syndrome and other adverse events (Table 2).

**Table 1**  
**Main characteristics of the studies included in the meta-analysis.**

Author (publication yr)	Country	Type of study	Population characteristics	Type of infection	No. of patient enrolled (LD/Non-LD)	Dosing regimen			Efficacy	Adverse events
						Loading dose	Comparator	Efficacy		
Level I evidence (properly designed RCT) Demirjian et al (2013)	United States	Single-center double-blind RCT	Children aged 2–18 yr, LD versus Non-LD ICU patients = 8 versus 6 Mean age (yr) = 8.63 ± 4.40 versus 8.76 ± 4.04 Mean weight (kg) = 34.9 ± 18.0 versus 29.7 ± 14.9 Mean CrCl (mL/min/1.73 m <sup>2</sup> ) = 206 ± 55 versus 196 ± 51	Sepsis, meningitis, pneumonia, bacteremia, SSTI, osteomyelitis, septic arthritis, fever and neutropenia	30/29	LD: 30 mg/kg, infused over 2 h MD: 20 mg/kg (<2 g), q8h, infused over 1 h	Non-LD: 20 mg/kg, infused over 2 h MD: 20 mg/kg (<2 g), q8h, infused over 1 h	LD versus non-LD Trough 15–20 mg/L at 8-h: 2/30 versus 0/29, Trough >20 mg/L at 8-h: 2/30 versus 2/29, AUC <sub>0-24 h</sub> (μg/mL/h): 446.5 ± 195.5 versus 434.0 ± 153.2	LD versus non-LD Red man syndrome: 14/30 versus 7/29 Doubling of baseline creatinine: 4/30 versus 1/29	
Rosini et al (2015)	United States	Single-center RCT	Adult ED patients, LD versus non-LD Mean age (yr) = 57.5 ± 14.5 versus 58.4 ± 15.6 Mean weight (kg) = 81.6 ± 19 versus 86.7 ± 20.3 Mean CrCl (mL/min/1.73 m <sup>2</sup> ) = 93.4 ± 28.1 versus 104.1 ± 55.8	Sepsis, Meningitis, Pneumonia, Bacteremia, SSTI, Osteomyelitis, Septic arthritis, Fever and neutropenia	50/49	LD: 30 mg/kg (<3.6g), MD: 15 mg/kg q12h for 3 doses infused at a rate less than 1000 mg/h	Non-LD: 15 mg/kg (<1.8g), MD: 15 mg/kg q12h for 3 doses infused at a rate less than 1000 mg/h	LD versus Non-LD Trough 15–20 mg/L at 12-h: 17/50 versus 1/49, Trough 10–15 mg/L at 8-h: 23/50 versus 6/49,	LD versus non-LD infusion reactions: 3/50 versus 2/49, Nephrotoxicity: 2/50 versus 3/49, Mortality: 1/50 versus 0/49 Hospital length of stay (d): 5.84 ± 4.8 versus 6.33 ± 5.6	
Level II evidence (multiple time series with or without intervention or dramatic results in uncontrolled experiments) Cheong et al (2012)	Malaysia	Retrospective study	Critically ill adult patients with MRSA infections All in ICU Mean age (yr) = 55.5 ± 16.6 Median weight (kg, IQR) = 68.4 Mean APACHE II score = 18.76 ± 8.18 Mean CrCl (mL/min/1.73 m <sup>2</sup> ) = 80.07 ± 9.11	MRSA infections such as bacteremia, endocarditis, osteomyelitis, meningitis and HAP	10/48	No details provided	No details provided	LD versus non-LD Clinical responder (improvement or culture negative): 9/10 versus 3/48	NR	
Tuong et al (2012)	Australia	Pre/postintervention study	Adult ICU patients Cohort 1 and Cohort 2 Mean age (yr) = 51 ± 18.1 and 60 ± 15.3 Mean weight (kg) = 73 ± 18.8 and 79 ± 17.0 CrCl ≥60 mL/min n (%) = 11/17 (62.4) and 28/61 (45.9) CrCl 30–59 mL/min n (%) = 0 and 14/61 (23.0) CrCl <30 mL/min n (%) = 1/17 (4.8) and 2/61 (3.3) CRR n (%) = 9/17 (42.9) and 17/61 (27.9)	Bums, surgery, infection/sepsis, respiratory distress, other	Cohort 1: 11/10 Cohort 2: 39/22	LD: 2 g, infused over 4 h MD: depend on patient clinical status	Non-LD: standard therapy MD: depend on patient clinical status	LD versus non-LD Trough <15 mg/L: 18/39 versus 16/22, Trough at 15–20 mg/L: 10/39 versus 4/22	Nephrotoxicity: total n = 4 (when trough >20 mg/L)	
Golonia et al (2013)	United States	Retrospective and prospective study	Adult ICU patients, pre-versus post nomogram Mean age (yr) = 61 ± 19.4 versus 60 ± 16.7 Mean weight (kg) = 75 ± 20.8 versus 77 ± 16.9 Mean CrCl (mL/min/1.73 m <sup>2</sup> ) = 79.9 ± 38.9 versus 86.2 ± 40.1	cardiac, medical, general surgery	60/57	LD, post nomogram implementation: 22.5–25 mg/kg (range 1000–2250 mg)	Non-LD: pre nomogram implementation: standard therapy (1000 mg q12h)	LD versus non-LD Trough <15 mg/L at initial pre-fourth dose: 17/60 versus 35/57 Trough 15–20 mg/L at initial pre-fourth dose n: 25/60 versus 11/57 Trough >20 mg/L at initial pre-fourth dose n: 18/60 versus 11/57	LD versus non-LD Nephrotoxicity: 11/60 versus 10/57	

(continued)

**Table 1**  
**(continued).**

Author (publication yr)	Country	Type of study	Population characteristics	Type of infection	No. of patient enrolled (LD/Non-LD)	Dosing regimen			Efficacy	Adverse events
						Loading dose	Comparator	Dosing regimen		
Rosini et al (2016)	United States	Retrospective Cohort study	Adult ED patients, LD versus non-LD Mean age (yr) = 64.8 ± 17.8 versus 64.0 ± 16.1 Mean weight (kg) = 79.5 ± 23.0 versus 106.2 ± 35.9 Mean dose (mg/kg) = 25.3 ± 3.8 versus 16.1 ± 2.9	NR	851/479	Non-LD: >20 mg/kg MD: not mentioned	Non-LD: <20mg/kg MD: not mentioned	NR	LD versus non-LD Nephrotoxicity: 49/851 versus 53/479	
Alvarez et al (2017)	Chile	Concurrent cohort study	Adult critically ill patients LD versus PPK-LD versus non-LD Mean age (yr) = 55.4 ± 19.4 versus 53.2 ± 17.3 versus 59.4 ± 15.8 Mean weight (kg) = 81.8 ± 16.0 versus 81.3 ± 19.1 versus 81.4 ± 21.0 Median APACHE II score = 20 versus 19 Clearance of vancomycin (L/h) = 2.8 versus 2.9 versus 3.0	Sepsis	23/18	LD: 25–30 mg/kg or LD based on population pharmacokinetic parameters of the critically ill patient MD: not mentioned	Non-LD: without LD (no details) MD: not mentioned	LD versus non-LD. Trough <15 mg/L within 24 h after first dose: 7/23 versus 16/18 LD versus non-LD. Trough 15–20 mg/L within 24 h after first dose: 9/23 versus 1/18 LD versus non-LD. Trough >20 mg/L within 24 h after first dose: 7/23 versus 1/18 Reached optimal AUC <sub>0–24</sub> : 5/11 (46) versus 11/12 versus 2/18	LD versus PPK-LD versus non-LD. Scr increased: 4/11 (36.3) versus 2/12 versus 6/18 no nephrotoxicity related with vancomycin was observed	
Wesolek et al (2017)	United States	Single-Centre Retrospective Cohort Study	MRSA infected patients, LD versus non-LD Mean age (yr) = 57.03 ± 18.06 versus 65.98 ± 16.91 Mean BMI (kg/m <sup>2</sup> ) = 23.63 ± 5.85 versus 25.61 ± 5.14 Mean APACHE II score = 21.44 ± 8.91 versus 22.97 ± 6.78 Mean dose (mg/kg) = 22.26 versus 14.87	Sepsis (due to MRSA)	37/87	LD: >20 mg/kg MD: not mentioned	Non-LD: <20 mg/kg MD: not mentioned	LD versus non-LD Median time to SIRS resolution (h): 67 versus 109. Clinical responder (improvement or culture negative): 30/37 versus 73/87 Time to negative blood culture (h): 102.25 ± 71.23 versus 99.60 ± 71.06, P = 0.557. Length of stay (h): 14.07 ± 10.03 versus 15.33 ± 8.60	LD versus non-LD Mortality: 7/37 versus 20/87	
Marvin et al	United States	Single-center Retrospective cohort study	Patients who received intravenous vancomycin, LD versus non-LD Mean age (yr) = 80 ± 19 versus 70 ± 22 Mean weight (kg) = 69 ± 24.7 versus 83.8 ± 35.5 Mean CrCl (mL/min) = 21.0 ± 9.7 versus 20.3 ± 9.5	NR	NR	LD: >20mg/kg MD: not mentioned	Non-LD <20 mg/kg MD: not mentioned	LD versus non-LD Trough 10–15 mg/L: 13/469 versus 37/458 LD versus non-LD Trough 15–20 mg/L: 236/469 versus 235/458	LD versus non-LD Mortality: 34/469 versus 63/458	

APACHE = Acute Physiology and Chronic Health Evaluation, AUC = area under concentration time curve, BMI = body mass index, CKD = chronic kidney disease, CrCl = creatinine clearance, CRRT = continuous renal replacement therapy, CT = confidence interval, ED = emergency department, HAP = hospital-acquired pneumonia, ICU = intensive care unit, LD = loading dose, MD = maintenance, MRSA = methicillin-resistant *Staphylococcus aureus*, Non-LD = non-loading dose use, NR = not reported, PPK = population pharmacokinetic parameters, RCT = randomized controlled trial, RR = relative risk, SIRS = systemic inflammatory response syndrome, SSTI = skin and soft-tissue infection, TOR = interquartile range.

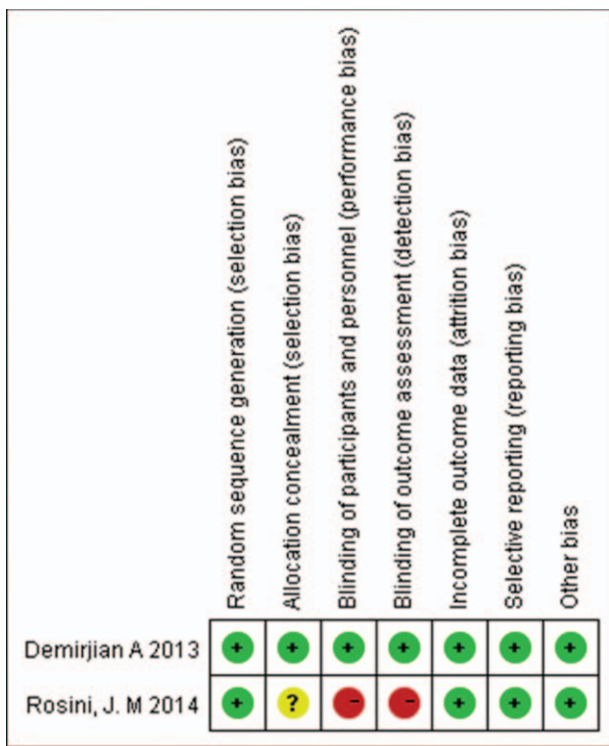


Figure 2. Risk of bias item for each included RCTs. RCTs = randomized controlled trials.

3.6. Mortality

Two studies reported the mortality following vancomycin loading dose administration (1051 patients), and the results showed that mortality was not significantly different between loading dose group and control group (OR=1.12; 95% CI=[0.78–1.62]; P=.54; I<sup>2</sup>=0%) (Fig. 6).

3.7. Clinical response

The clinical response referred to a response of the patient to vancomycin administration. Patients who responded clinically with negative bacterial culture at the end of therapy and those who responded clinically but without culture result at the end of

therapy were all considered to have clinical response. Only 2 cohort studies reported negative blood culture or clinical response. The clinical response was numerically higher in loading dose group than in control group. However, no significant difference was found between the 2 groups (OR=1.28; 95% CI=[0.33–5.03]; P=.72; I<sup>2</sup>=37%) (Fig. 7).

4. Discussion and conclusions

According to the United States Food and Drug Administration, the section of dosage and administration, the normal daily intravenous dose of vancomycin is 2g divided either as 500 mg every 6 hours or 1g every 12 hours for patients with normal renal function. The label of Vancomycin Injection approved by FDA does not mention the usage of vancomycin loading dose.<sup>[23]</sup> However, in several clinical practice guidelines published in Japan and the United States, loading dose is recommended for seriously ill patients with suspected MRSA infection (eg, those with sepsis, meningitis, pneumonia, or infective endocarditis).<sup>[4,6]</sup> Several studies<sup>[16,21]</sup> reported better clinical outcomes in patients treated with vancomycin loading dose. However, due to the lack of large size samples and well-controlled design, these studies were not enough to confirm the efficacy and safety of vancomycin loading dose. Adequate studies and statistical analysis remain needed to support the clinical efficacy of vancomycin loading dose. The results of our systematic review and meta-analysis indicate that vancomycin loading dose therapy may be a better treatment for patients who have serious infections caused by susceptible strains of MRSA, compared with nonloading dose therapy. To our knowledge, this is the first systematic review to assess the clinical efficacy and safety of vancomycin loading dose.

We found that loading dose group can achieve optimal trough concentration significantly better than nonloading dose group in pooled studies. Soto et al<sup>[24]</sup> found that standard vancomycin dose of 500 mg every 6 hours is sub-therapeutic in critically ill patients. Mohammadi's<sup>[25]</sup> results suggest that 15 mg/kg vancomycin loading dose should be considered in critically ill patients with suspected Gram-positive infections. In most cases, when the loading dose is used, the optimal trough concentrations of 15 to 20 mg/L can be achieved in adults within 24 hours before the second dose, no matter the dosing interval is 6, 8, or 12 hours. As for children, Demirjian's study<sup>[15]</sup> shows that the compliance rate of optimal trough concentration is higher in loading dose group than in control group, but the difference was not statistically

Table 2  
Newcastle–Ottawa scale for assessing the quality of included non-RCTs.

Study	Selection			Demonstration that outcome of interest was not present at start of study	Comparability		Exposure		Score
	Representation of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Cheong JY/2012	✓	✓	✓	✓	✓✓				6
Wesolek JL/2017	✓	✓	✓	✓	✓✓		✓	✓	8
Golenia BS/2012	✓	✓	✓	✓	✓	✓	✓		8
Rosini JM/2016	✓	✓	✓	✓	✓✓	✓			7
Marvin JL/2019	✓	✓	✓	✓	✓✓	✓	✓		8
Álvarez O/2017	✓	✓	✓	✓	✓✓	✓	✓	✓	9
Truong J/2012	✓	✓	✓	✓	✓✓	✓	✓	✓	9

RCTs=randomized controlled trials.

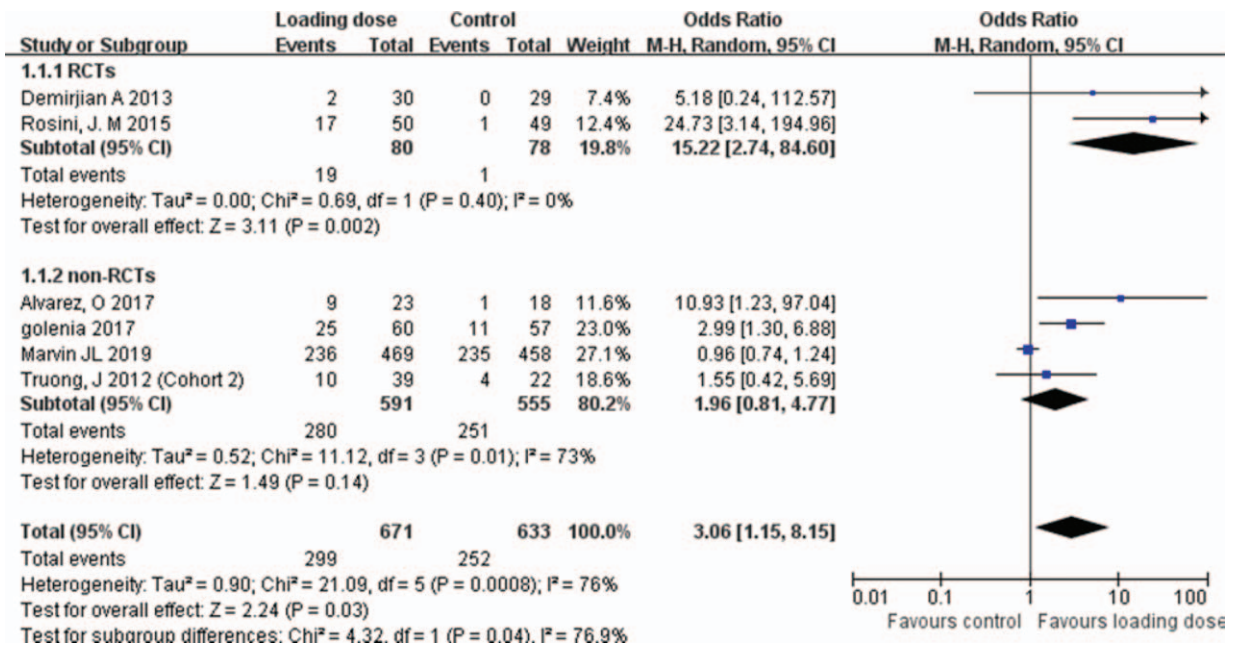


Figure 3. Achievement of therapeutic concentration with vancomycin loading dose versus control.

significant. Regarding hospitalized hemodialysis patients, Nekidy et al<sup>[26]</sup> conducted a prospective observational cohort study in adult patients with chronic kidney disease who were hospitalized for hemodialysis. They found that among 24 patients who achieved the recommended pre-hemodialysis serum vancomycin concentration (15–20 mg/L), 14 patients received a loading dose of 15 to 20 mg/kg. The finding of this study favors the use of vancomycin loading dose of 15 to 20 mg/kg. Previously, Wang<sup>[27]</sup> reported that loading dose can accelerate the build-up of

vancomycin serum trough concentration to above 8 mg/L within the first 24 to 48 hours to ensure the best therapeutic outcome.

Nephrotoxicity is one of the main adverse reactions of vancomycin. Considering that the loading dose may bring a higher risk of nephrotoxicity, it is uncertain whether the vancomycin loading dose is safe for clinical application. Our meta-analysis showed that nephrotoxicity was even lower in the loading dose group than in control group, indicating that the loading dose does not associate with increased nephrotoxicity.

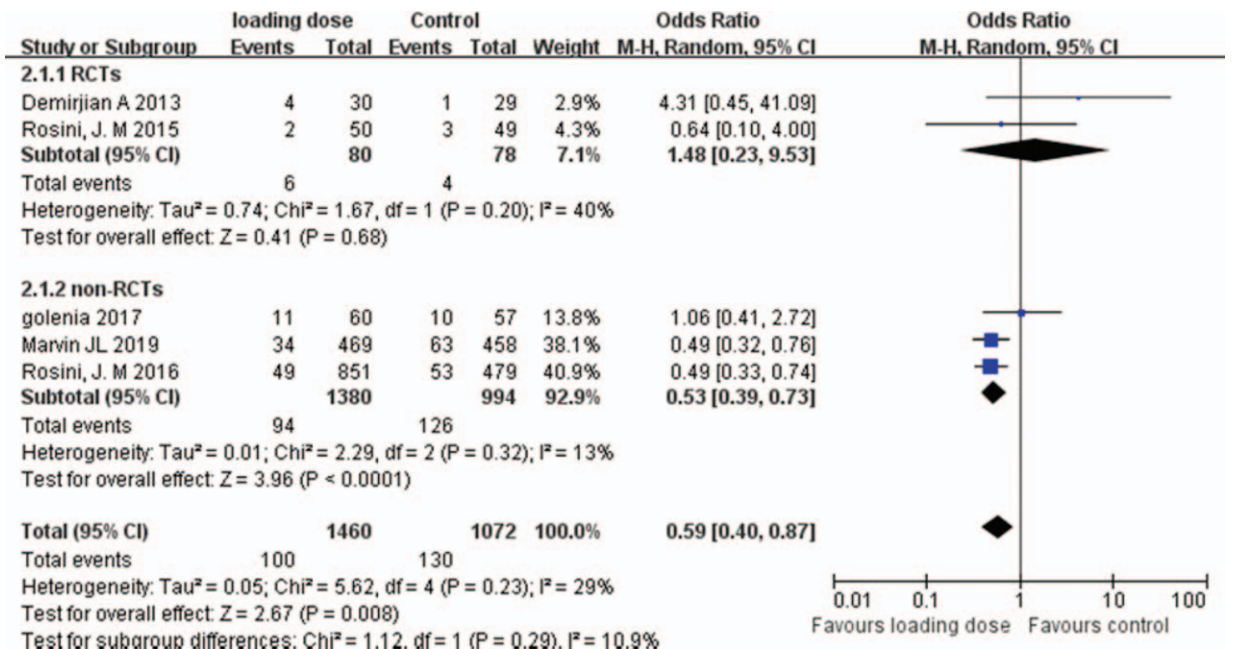


Figure 4. Nephrotoxicity with vancomycin loading dose versus control.

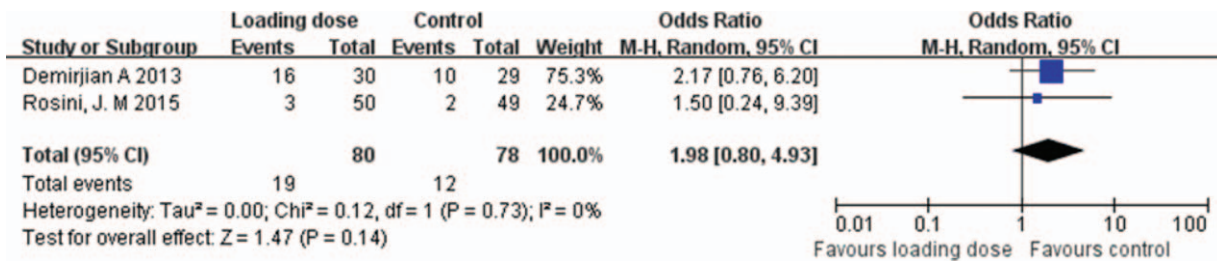


Figure 5. Other adverse events with vancomycin loading dose versus control.

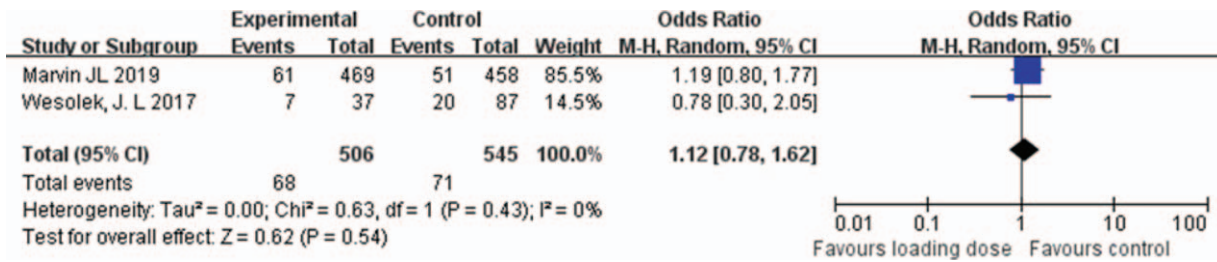


Figure 6. Mortality with vancomycin loading dose versus control.

We found that loading dosage is only associated with the reduction of nephrotoxicity in non-RCTs subgroup, while no significant difference was found in RCTs group. There may be 2 reasons for this result. First, in the non-RCTs studies, clinicians may be able to pay more attention to the patients receiving loading dose and take renal protective measures. However, the relevant data are not available from the original studies. Second, most of the patients in non-RCTs studies were ICU patients and sepsis patients with poor basic conditions and may have a rapid progress of disease. In this case, the decline in renal function is more likely to be related to the progression of the disease. Compared with conventional-dose, loading dose of vancomycin can ensure the rapid achievement of target drug concentration and produce better antibacterial results. Effective control of infection might delay the progression of renal damage.

Higher dose of vancomycin is also considered to cause other adverse effects. Our meta-analysis indicated that the occurrence rate of adverse events in loading dose group was not significantly higher than that of the control group. FDA advised that vancomycin should be administered over a period of at least 60 minutes to avoid rapid-infusion-related reactions. For patients' safety, prolonged infusion time is preferred when using vancomycin loading dose. For example, Rosini et al<sup>[15]</sup>

recommended that vancomycin should be infused at a rate less than 1000mg/h. Demirjian et al<sup>[14]</sup> suggested that vancomycin should be infused over 1 hour to prevent infusion-related reactions. With prolonged infusion time, the incidence of infusion-related reactions seems to be reduced in loading dose group. The bactericidal effect of vancomycin is time-dependent and has long post-antibiotic effect. Thus, maintaining an effective trough concentration can improve the bactericidal efficacy. Vuagnat et al<sup>[28]</sup> conducted a cohort study to compare the efficacy and safety of intermittent vancomycin infusion (IVI) and continuous vancomycin infusion (CVI) in high-dose therapy. With respect to pharmacokinetics, the plateau concentration of vancomycin in CVI group was significantly higher than the mean trough vancomycin concentration in IVI group. Therefore, prolonged infusion with loading dose may increase trough concentration of vancomycin compared with normal infusion time.

In addition, there was no significant difference in mortality and clinical response between the traditional dose group and the load dose group, which also confirmed that the loading dose of vancomycin is safe, and could be used as an alternative treatment for bacterial infection.

The present systematic review had some limitations and should be viewed prudently. First, only 2 RCTs were included with

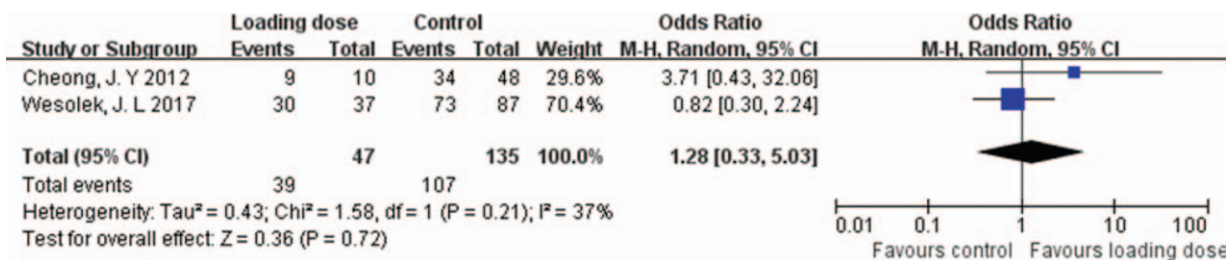


Figure 7. Clinical response with vancomycin loading dose versus control.



limited number of cases, and more RCTs are needed to validate the results. Second, some outcomes of included studies were not provided. For example, only 2 studies reported the clinical response and mortality, which may reduce the power of the statistical analysis. In addition, heterogeneity existed in some of the analyses, even when subgroup analysis was conducted.

In conclusion, the use of vancomycin loading doses can significantly increase the achievement of therapeutic concentration. In terms of safety, loading dose reduces the incidence of nephrotoxicity and does not increase the incidence of other adverse events. Based on the available data, loading dose of vancomycin is proved to be a safe and effective therapeutic option for critically ill patients. High-quality large-scale RCTs remain needed to further validate the safety and efficacy of vancomycin loading dose.

### Author contributions

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### References

- Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis* 2006;42(Suppl 1):S35–9.
- Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52:285–92.
- Ackerman BH, Vannier AM, Eudy EB. Analysis of vancomycin time-kill studies with *Staphylococcus* species by using a curve stripping program to describe the relationship between concentration and pharmacodynamic response. *Antimicrob Agents Chemother* 1992;36:1766–9.
- Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009;66:82–98.
- Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet* 2004;43:925–42.
- Matsumoto K, Takesue Y, Ohmagari N, et al. Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. *J Infect Chemother* 2013;19:365–80.
- 2011;Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. 52:975–81.
- 2013;Ne H, JD T, Wj M, et al. Vancomycin AUC/MIC ratio and 30-day mortality in patients with *Staphylococcus aureus* bacteremia. 57:1654–63.
- Gawronski KM, Goff DA, Brown J, et al. A stewardship program's retrospective evaluation of vancomycin AUC24/MIC and time to microbiological clearance in patients with methicillin-resistant *Staphylococcus aureus* bacteremia and osteomyelitis. *Clin Ther* 2013;35:772–9.
- Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the infectious diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. *Clin Infect Dis* 2009;49:325–7.
- Mei H, Qing Y. The Clinical Efficacy of Vancomycin Loading Dose: A Systematic Review and Meta-Analysis. PROSPERO 2018 CRD42018093927; 2018. Available at: [http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42018093927](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018093927). Accessed November 5, 2018.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- Allen TW. Guide to clinical preventive services. Report of the US Preventive Services Task Force. *J Am Osteopath Assoc* 1991;91:281–9.
- Demirjian A, Finkelstein Y, Nava-Ocampo A, et al. A randomized controlled trial of a vancomycin loading dose in children. *Pediatr Infect Dis J* 2013;32:1217–23.
- Rosini JM, Laughner J, Levine BJ, et al. A randomized trial of loading vancomycin in the emergency department. *Ann Pharmacother* 2015;49:6–13.
- Cheong JY, Makmor-Bakry M, Lau CL, et al. The relationship between trough concentration of vancomycin and effect on methicillin-resistant *Staphylococcus aureus* in critically ill patients. *S Afr Med J* 2012;102:616–9.
- Truong J, Levkovich BJ, Padiglione AA, et al. Simple approach to improving vancomycin dosing in intensive care: a standardized loading dose results in earlier therapeutic levels. *Intern Med J* 2012;42:23–9.
- Golenia BS, Levine AR, Moawad IM, et al. Evaluation of a vancomycin dosing nomogram based on the modification of diet in renal disease equation in intensive care unit patients. *J Crit Care* 2013;28:710–6.
- Rosini JM, Davis JJ, Muenzer J, et al. High single-dose vancomycin loading is not associated with increased nephrotoxicity in emergency department sepsis patients. *Acad Emerg Med* 2016;23:744–6.
- Álvarez O, Plaza-Plaza JC, Ramirez M, et al. Pharmacokinetic assessment of vancomycin loading dose in critically ill patients. *Antimicrob Agents Chemother* 2017;61:e00280-17.
- Wesolek JL, McNorton K, Delgado G, et al. Effect of vancomycin initial dosing on time to systemic inflammatory response syndrome resolution in patients with methicillin-resistant *Staphylococcus aureus* bacteremia. *J Chemother* 2018;30:101–6.
- Marvin JL, Levine BJ, Papas M, et al. An evaluation of the incidence of nephrotoxicity after a loading dose of vancomycin in patients with severe renal impairment. *J Emerg Med* 2019;56:701–8.
- USP. Vancomycin Injection. FDA 2017 NDA 050671; 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/050671s024lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050671s024lbl.pdf); [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/050671s024lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050671s024lbl.pdf). [Accessed on October 2017]
- Soto J, Sacristan JA, Alsar MJ. Necessity of a loading dose when using vancomycin in critical-ill patients. *J Antimicrob Chemother* 1991;27:875.
- Mohammed I, Descloux E, Argaud L, et al. Loading dose of vancomycin in critically ill patients: 15 mg/kg is a better choice than 500 mg. *Int J Antimicrob Agents* 2006;27:259–62.
- El Nekidy WS, El-Masri MM, Umstead GS, et al. Factors influencing vancomycin loading dose for hospitalized hemodialysis patients: prospective observational cohort study. *Int J Antimicrob Agents* 2012;65:436–42.
- Wang JT, Fang CT, Chen YC, et al. Necessity of a loading dose when using vancomycin in critically ill patients. *J Antimicrob Chemother* 2001;47:246.
- Vuagnat A, Stern R, Lotthe A, et al. High dose vancomycin for osteomyelitis: continuous vs. intermittent infusion. *J Clin Pharm Therap* 2004;29:351–7.